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Original article

Investigate the effect of solvents on wet granulation of microcrystalline cellulose using hydroxypropyl methylcellulose as a binder and evaluation of rheological and thermal characteristics of granules

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ABSTRACT

Wet granulation is the most commonly used technique in the pharmaceutical industry for delivering oral solid dosage forms. In wet granulation, the binder solvent is one of the critical factors affecting granule properties. In the current study, an attempt was made to investigate the effect of solvents (aqueous and hydro-alcoholic) on thermal and flow properties of Microcrystalline Cellulose (MCC) granules prepared using two different grades of Hydroxypropyl Methylcellulose (HPMC), which served as an effective binder. The granulation endpoint was evaluated using thermal effusivity sensor. Rheometer and Modulated Differential Scanning Calorimetry (mDSC) was used to study the flow and thermal properties of wet and dried granules. Furthermore, physical characterization was carried out by granule strength, particle size distribution and tablet hardness for all granules under the study. Thermal effusivity sensor results indicate 55% w/w concentration of binder solution as the endpoint by measuring thermal effusivity for both binders. Additionally, powder rheometer results show that the wet granules of hydro-alcoholic batches show greater resistance to flow whereas the dried granules display excellent flow characteristics as evident from Basic flowability energy values and specific energy values. Permeability results suggest that the granules formed with hydro-alcoholic binder solvent exhibit better porosity and permeability. Tablet hardness data showed that tablets formulated using hydro-alcoholic solvent granules have greater hardness than tablets formulated using water based solvent granules. The granule strength for water based granules is relatively higher than that of hydro-alcoholic based granules. mDSC thermograms show a sharp rise in enthalpy value at 55% w/w binder solution which is indicative of a more significant amount of solvent being present on the surface of granules and formation of optimal granules. To summarize, we have determined a technique to measure endpoint determination and simultaneously investigate the role of solvent systems on the rheology of MCC granules, which could assist in selecting an appropriate solvent system for granulation.

1. Introduction

Since decades, granulation is operational as a critical size enlargement process for powder agglomeration in tablet manufacturing. Dry granulation (Kleinebudde, 2004), melt granulation (Gajera et al., 2006; Dugar et al., 2016) and wet granulation (Chaturvedi et al., 2018) are some of the most common techniques utilized for granulation in the pharmaceutical industry. However, in pharmaceutical tablet production, wet granulation is the most frequently used process consisting of agglomerating powder particles with a liquid binder, in a fluidized bed, high shear mixer or low shear mixer (Iveson et al., 2001). All required features for compression, namely a good flow, appropriate compactibility and uniform drug distribution can be achieved using wet granulation and hence it is extensively employed granulation technique (Sinko, 1997).

In wet granulation, it is imperative to determine the optimum quantity of binder solution as granule properties affect dosage form performance (Achanta et al., 1997; Leuenberger et al., 2009). The end-point in wet granulation process is a point at which a formulator achieves a target particle size, after addition of an

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optimum amount of granulating fluid (Dave et al., 2012). The rapidity with which granulation proceeds, makes endpoint determination difficult and further necessitates monitoring of the process (Levin, 2006). The potential for various methods to determine the end point of wet granulation has been reviewed extensively (Jørgensen, 2004). In the present article, an end-point determination is carried out by one such technique, namely Thermal Effusivity, which is an emerging Process Analytical Technology (PAT) tool for optimizing wet granulation (Fariss et al., 2006).

Tablet production is an intricate process consisting of several steps, each of which subjects the powder to a specific set of environmental conditions. It is therefore essential to have an understanding of rheological characteristics of granules, which include bulk, dynamic and shear properties (Kristensen and Schaefer, 1987; Parikh, 2016). Thus, to study the rheological properties of granules, FT4 powder rheometer was used (Freeman, 2004).

Diluents or bulking agents serve as the vital component of a dosage form. Microcrystalline cellulose is one such widely used diluent in pharmaceuticals due to its diverse characteristics based on different particle size. The model diluent selected for this study was MCC 105 due to its small particle size, high cohesiveness, and superior compactibility, making it an attractive candidate for size enlargement process using wet granulation (Sun, 2008; Patel and Podczeck, 1996). Furthermore, granulating solvent significantly affects the granule properties. Changing the solvent system leads to a change in wettability and solubility of formulation constituents, and thus influences binder distribution, which in turn affects the granule strength and porosity (Wikberg and Alderborn, 1993; Shah et al., 1996). In the pharmaceutical industry aqueous, hydro-alcoholic, and alcoholic solvent systems are widely used. Therefore, in the present study, aqueous and hydro-alcoholic solvent systems are employed for wet granulation. Hydroxypropyl methylcellulose (HPMC) cellulose ethers are water-soluble polymers derived from cellulose, used as vital binding ingredients in the pharmaceutical processes. HPMC polymers are considered as versatile binding agents as they work well with soluble and insoluble drugs and at high and low dosage levels. Methocel™ K4M CR and K100M CR are selected based on their utilization in wet granulation to formulate hydrophilic matrix systems, one of the widely used means for controlled drug delivery in solid oral dosage (Biswas et al., 2014; Jain, 2008). The viscosity of the binder is another important parameter which has to be taken into account during granulation since the binder viscosity impacts the strength of the resulting granules (Chitu et al., 2011; Keningley et al., 1997; Knight, 2004; Johansen and Schæfer, 2001; Lieberman and Pharmaceutical, 1980). L. Stubberud et al. described that an increase in viscosity has a beneficial effect on the granulation, up to a specific critical value (Stubberud et al., 1996).

The present study focuses on comparing rheological properties, thermal properties and granule strength of MCC granules by using two grades of HPMC as a liquid binder, prepared with water and hydro-alcoholic solvent systems, whereby studying the effect of both, solvent and binder viscosity on granules produced by low shear granulator.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Avicel® PH 105, lot # 51207C) was received as a generous sample from FMC Biopolymer Corp (Philadelphia, PA). HPMC K100M CR (Methocel™ K100M CR, Lot # ZG12012N01) and HPMC K4M CR (Methocel™ K4M CR, Lot # ZG07012N02) used as binders, were kindly supplied by Dow Chemicals (Midland, Michigan, USA.). Deionized water (Barnstead Nanopure model # 7119, Thermoscientific system, Waltham, MA) was collected above 13 mΩ·cm and Ethyl Alcohol 190 Proof USP (Lot # C1202101) purchased from Pharmaco - Aaper (Brookfield, CT, USA), were used as solvents for the current study.

2.2. Binder solution preparation

Four types of binder solutions were prepared using two types of HPMC binders, HPMC K100M CR (Methocel™ K100M CR and HPMC K4M CR (Methocel™ K4M CR) with deionized water and hydro-alcoholic mixtures as solvents (Table 1). The binder solutions with de-ionized water were prepared using the hot-cold method. About 35 g of water was heated to 80–90 °C and 0.5 g of the binder was added to the heated water and mixed. Later, volume was adjusted using cold water to form a 0.5% w/w binder solution. The hydro-alcoholic binder solution was prepared by using 50 parts of water and 50 parts of ethyl alcohol (50:50), mixed with 0.5 g of the binder forming a 0.5% w/w binder solution. The viscosity of binder solutions was a determined using RV spindle with Brookfield Viscometer (DV-II+ Pro, Middleboro, Massachusetts, USA).

2.3. Preparation of wet and dried granules

Preliminary screening experiments were performed to determine the optimum amount of binder solution for MCC PH 105 batches. They were carried out by using 10 g of MCC granulated in a mortar and pestle with different binder solutions added in a geometric progression starting at 5% w/w until a drastic increase in effusivity reading was observed. For large scale studies, 700 g batches were prepared following optimum endpoint range obtained from thermal effusivity measurements of small-scale batches (10 g). The granules were prepared using a lab scale Cuisinart mixer (East Windsor, NJ) with a batch size of 700 g of MCC PH 105 with 45, 50, 55%w/w of all four binder solutions. The granulator was set at 100 rpm for 3 min, and the binder solution was added at a constant rate. The end-point of mixing was also determined using the thermal effusivity sensor (C-therm ESP, New Brunswick, Canada). The wet granules formed at the end of the granulation were subjected to thermal evaluation using Modulated Differential Scanning Calorimetry (mDSC) and powder rheometer for additional testing. The remaining granules were passed through sieve # 14 and dried in a tray dryer at 60 °C until ≤5% w/w moisture was observed. Percentage of moisture retained was determined using Loss On Drying (LOD) (Ohaus, MB 200, Pinebrook, NJ). After drying, all the batches were subjected to thermal and rheological characterization.

2.4. Thermal effusivity measurements

Thermal Effusivity is a non-destructive method to determine the end point of wet granulation using intrinsic properties such as heat capacity, thermal conductivity, and density of the material/material mixture. Effusivity measurements were conducted using the thermal conductivity (TCi–D12) Probe (Mathis Instruments, Fredericton, NB, Canada) (Fig. 1) which was calibrated before testing, using polymethyl siloxane. Samples were placed in direct contact with the probe and were as flat as possible to ensure maximum connection with the probe, which supplies heat to the sample (<2 K) for about 0.8–1 s. The sensor detects interfacial heat flow change from the materials based on their intrinsic properties, which induces a voltage drop, and this is representative of its thermophysical property (Kleinebudde, 2004). Preliminary trials were carried out with small-scale batches of 10 g each. Based on initial experiments, lab scale batches of 700 g were prepared by adding 45% w/w (572.3 g), 50% w/w (700 g) and 55% w/w (855.4 g) of each binder solution, and were exposed to the TCi – D12 probe, to determine their effusivity reading.

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